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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,079	09/16/2003	Nicholas G. Bacopoulos	24852-501 CIP5	6072

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,079	BACOPOULOS ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,32-35,37-45,47,49-61,63-68,70 and 71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32-35,37-45,47,49-61,63-68,70 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 30, 32-35, 37-45, 47, 49-61, 63-68 & 70-71 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 4/16/2007 and Information Disclosure Statements filed 4/18/2007, 5/23/2007 and 6/21/2007 have been received and entered into the application. Accordingly, claims 30, 32, 34-35, 37-38, 47, 49 and 51-56 have been amended and claims 46, 62 and 69 have been cancelled. Also, as indicated in the attached USPTO Form 1449, the Examiner has considered the cited references.

The amendments and Applicants' remarks have overcome the rejections not reiterated herein from the previous office action. Such rejections are hereby *withdrawn*. The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

In light of the new rejections being applied against the pending claims, this Office Action is **Non-Final**.

Response to Arguments

Applicant's arguments filed 4/19/2007 have been fully considered but they fail to persuade the Examiner of an error in his determination that the claimed invention is obvious over Richon *et al.* in view of Rubartelli *et al.* and Richon *et al.* and Rubartelli *et al.* in view of Kelly *et al.*

Firstly, Applicants argue that Richon *et al.* is fatally deficient because the reference refers to the use of HDAC inhibitors in a laundry list of TRX-mediated diseases and Richon *et al.* do not mention treatment of lymphoma. Further, Applicants argue that Richon *et al.* do not teach or

suggest the claimed dosages and dosing schedules for treating diffuse large B-cell lymphoma. With respect to Applicants' assertion that Richon *et al.* do not explicitly teach the treatment of B-cell lymphoma, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the Examiner has combined Richon *et al.* with Rubartelli *et al.*, who provide the nexus between TRX and B-cell lymphomas. With respect to Applicants' assertion that Richon *et al.* do not teach or suggest the claimed dosages and dosing schedules, the reference provides ample teaching with respect to oral administration of HDAC inhibitors for the treatment of TRX-mediated diseases. For example, oral dosages between about 2 mg and about 2000 mg per day (specifically 2, 20, 200, 400, 800, 1200, 1600 and 2000 mg per day) are disclosed (page 19, ¶ [0181]). Further, the total amount of HDAC inhibitor can be administered in multiple doses, such as twice, three or four times per day (*id.*). These doses and dosing schedules reasonably suggest and motivate the instantly claimed doses and dosing schedules. With respect to the Rubartelli *et al.* reference, Applicants' argue that the reference does not teach or suggest the claimed doses and dosing schedules for oral treatment of patients with diffuse large B-cell lymphoma. However, when combined with Richon *et al.*, the references provide one skilled in the art with the teaching and motivation to administer SAHA for the treatment of TRX-mediated diseases, including B-cell lymphoma. Finally, it is well within the purview of the skilled artisan to adjust dosing schedules so as to maximize efficacy while minimizing toxicity. Once a general administration regimen is disclosed in the prior art, it is not unobvious to find the optimal dose and dosing schedule within the guidelines of the prior art teachings.

Applicants argue that Kelly *et al.*, when combined with Richon *et al.* and Rubartelli *et al.*, does not cure the deficiencies of the primary references. For example, Applicants argue that Kelly *et al.* is directed to optimizing intravenous dosing for SAHA. While Applicants' September 19, 2006 Amendment demonstrating unexpected increase in half life compared to IV delivery of SAHA has been duly considered, the Examiner respectfully submits that Kelly *et al.* was not used to obviate oral versus IV dosing. Kelly *et al.* is provided as evidence that optimization of administration schedules of SAHA is well within the level of ordinary skill in the art. Richon *et al.* provide ample suggestion and motivation to orally administer SAHA and further suggest that such administration is amiable to optimization.

Applicants' arguments with respect to claims 30, 32-35, 37-47 and 49-71 (Breslow *et al.* in view of Richon *et al.*) have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 30, 32-35, 37-40, 47, 49-56, 63-66 and 69-70 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Richon *et al.* (US 2003/0235588 A1; Published Dec. 25, 2003) (cited by applicants in IDS filed 9/13/2005)[1] in view of Rubartelli *et al.* (Cancer Research, 1995, vol. 55, pages 675-680).

The instant claims are drawn to a method of treating diffuse B-cell lymphoma comprising oral administration of SAHA.

Richon *et al.* disclose methods of treating thioredoxin (TRX)-mediated diseases by administering to a subject in need of such treatment a therapeutically effective amount of a histone deacetylase (HDAC) inhibitor or a pharmaceutically acceptable salt or hydrate thereof (Abstract). Elevated levels of TRX have been found in cancer. As such, TRX can "stimulate proliferation of a wide variety of cancer cell lines and inhibit apoptosis in cells over expressing the protein" (page 1, ¶ [0007]). The invention discloses the use of HDAC inhibitors that can alter the expression of a TRX-binding protein (*e.g.* TRX-binding protein-2 or TBP-2), which in turn can lead to altered TRX/TBP-2 cellular binding interaction, resulting in an increase or decrease in the level or activity of cellular TRX (pages 1-2, ¶ [0011]). Thus, the invention relates to the use of HDAC inhibitors in a wide variety of TRX-mediated diseases and conditions, including diseases characterized by cellular hyperproliferation (*id.*). The inventors discovered that HDAC inhibitors induce expression of a TRX-binding protein, which is

[1] Richon *et al.* qualifies as prior art under 35 U.S.C. § 102(e) as it claims priority to U.S. Provisional Application No. 60/357,383, filed Feb. 15, 2002.

associated with a decrease in the level or activity of TRX resulting from interaction of TRX with the TRX-binding protein (page 2, ¶ [0012]). HDAC inhibitors, therefore, can be used to treat diseases characterized by "an increased level or activity of TRX" (page 2, ¶ [0013]). HDAC inhibitors effective at treating TRX-mediated diseases include hydroxamic acid derivatives (page 2, ¶ [0021]), including the instantly claimed SAHA (*id.* at ¶ [0023] and page 3, ¶ [0030]). Pharmaceutically acceptable salts of HDAC inhibitors are recited at page 17, ¶ [0156]. Hydrates of HDAC inhibitors are recited at page 17, ¶ [0157]. HDAC inhibitors of the invention can be administered in oral forms including tablets, capsules, pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions (page 18, ¶ [0176]). Oral dosages of the HDAC inhibitors can range between about 2 mg to about 2000 mg per day and specific oral dosages of 2, 20, 200, 400, 800, 1200, 1600, and 2000 mg per day are disclosed (page 19, ¶ [0181]). The reference thus discloses the oral dosages of SAHA instantly claimed. The total daily amount of HDAC inhibitor can be administered in multiple doses, such as twice, three, or four times per day (*id.*). The oral formulations can be in the form of tablets or capsules and combined with pharmaceutically acceptable inert carriers, including microcrystalline cellulose (page 20, ¶ [0191]). In addition, suitable binders, lubricants and disintegrating agents can be included in the formulation (*id.*). Suitable disintegrating agents include the instantly claimed sodium croscarmellose (*id.*). Suitable lubricants include the instantly claimed magnesium stearate (*id.*). Thus, Richon *et al.* disclose methods of administering the instantly claimed HDAC inhibitor in the doses and formulations instantly claimed. The reference further discloses methods of treating TRX-mediated diseases. The reference does not explicitly disclose the treatment of diffuse B-cell lymphoma by orally administering SAHA.

However, Rubartelli *et al.* provide the nexus between TRX and B-cell lymphomas and further provide the motivation to use the methods disclosed in Richon *et al.* to treat B-cell lymphomas. The reference discloses that exogenous TRX exerts cytokine activities, such as induction of cell proliferation in neoplastic T and B lymphocytes (page 675, left column, second full paragraph). Further, TRX is identical to eosinophil cytotoxicity enhancing factor and to a B-cell hybridoma-derived factor able to induce proliferation and differentiation of B-chronic lymphocytic leukemia cells (*id.*). Secretion of TRX is developmentally regulated in normal B and T lymphocytes and is more abundant in activated than in resting lymphocytes (*id.*). Thus, TRX has growth-promoting activity in neoplastic B-lymphocytes.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art discloses methods of treating TRX-mediated diseases comprising oral administration of HDAC inhibitors in the doses instantly claimed (Richon *et al.*). The prior art also provides the nexus between TRX and growth-promotion of neoplastic B-lymphocytes (Rubartelli *et al.*).

The prior art does not *explicitly* disclose the treatment of B-cell lymphoma comprising the oral administration of SAHA. However, given the scope and contents of the prior art, the

instantly claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

The level of ordinary skill in the art is that of an M.D., Ph.D. or pharmacist. The skilled artisan would have been aware that B-cell lymphoma could be characterized as a TRX-mediated disease given the disclosure of Rubartelli *et al.*

It is well known in the art that SAHA is capable of inducing tumor cell growth arrest, differentiation and/or apoptosis (Specification, page 4, lines 29-31). As such, one skilled in the art would have appreciated that the methods described in Richon *et al.* would be useful in the treatment of cancers wherein TRX is implicated. In fact, Richon *et al.* contemplate such a treatment of diseases characterized by cellular hyperproliferation (*e.g.* cancer).

Given the above analysis, the instantly claimed methods of treating B-cell lymphoma would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Richon *et al.* disclose the instantly claimed HDAC inhibitor as well as oral formulations and doses commensurate in scope with the instant claims. Rubartelli *et al.* provide the nexus and motivation to use the methods disclosed in Richon *et al.* to treat B-cell lymphomas. As such, the skilled artisan would have had the means and motivation to treat B-cell lymphoma with an oral formulation of the HDAC inhibitor, SAHA.

Claims 41-45, 57-61, 67-68 and 71 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Richon *et al.* and Rubartelli *et al.* as applied to claims 30, 32-35, 37-40, 47, 49-56, 63-66 and 69-70 above, and further in view of Kelly *et al.* (Proc. American Society of Clinical Oncology, 2001, 20:87a, Abstract No. 344) (cited by applicants in IDS filed 6/9/2005).

This instant claims recite administration of oral SAHA three to five day per week and for 14 consecutive days in a 21 day schedule.

Richon *et al.* and Rubartelli *et al.* disclose as discussed *supra*. The combined references do not *explicitly* disclose the specific administration schedules instantly claimed.

However, Kelly *et al.* is provided as evidence that optimizing administration schedules of SAHA is well within the level of ordinary skill in the art and is therefore routine optimization. The reference discloses the optimization of dosing regimes for intravenous SAHA. SAHA was administered to patients at varying doses as a 2-hr. IV infusion for three consecutive days every 21 days and for five consecutive days for 1-3 weeks.

The skilled artisan would have been highly motivated to determine the optimal dose and schedule of administration of SAHA for the treatment of B-cell lymphoma. It is noted that optimization of drug dosing and scheduling is routine in the art of cancer therapy. For example, Phase I and Phase II clinical trials both focus on determining such parameters, as well as determining the efficacy and toxicity of the administered drug. Thus, the instantly claimed dosing regimes of oral SAHA would have been *prima facie* obvious as they would have been readily determined by the skilled artisan from routine optimization of the methods and dosing schedules disclosed in Richon *et al.*

Claims 30, 32-35, 37-47 and 49-71 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Breslow *et al.* (U.S. Patent No. 5,700,811; Issued Dec. 23, 1997) (cited by applicants in IDS filed 4/6/2004) in view of The Merck Manual of Diagnosis and Therapy, 17th

Edition (1999, Whitehouse Station, N.J., pages 958-962) and Richon *et al.* (US 2003/0235588 A1; Published Dec. 25, 2003) (cited by applicants in IDS filed 9/13/2005).

Breslow *et al.* disclose methods of selectively inducing terminal differentiation of neoplastic cells and, thereby inhibiting proliferation of such cells, comprising administration of compounds that encompass the instantly claimed SAHA (Abstract). SAHA is explicitly disclosed at col. 29, lines 53-60 and in Table 1, Compound 3. The invention provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells which comprises administering to said patient an effective amount of any of the compounds disclosed in the patent (col. 15, lines 14-20). The administration of the compounds may be effected orally or parenterally (*id.* at lines 28-29). The administration of the compounds "must be performed continuously for a prolonged period of time, such as for at least 3 days and preferably more than 5 days (*id.* at lines 29-32). In a preferred embodiment, the administration is effected continuously for at least 10 days and is repeated at intervals. For example, administration may be at intervals as short as 5-10 days, up to about 25-30 days (*id.* at lines 36-39). The optimal interval period will vary depending on the type of patient and tumor (*id.* at lines 39-40).

The Merck Manual is provided as evidence that diffuse B-cell lymphomas are characterized by proliferation of neoplastic cells and are thus reasonably suggested by Breslow *et al.* For example, Non-Hodgkin's Lymphomas are characterized as "malignant monoclonal proliferation of lymphoid cells in sites of the immune system" (page 958). Further, diffuse large cell lymphomas are characterized as intermediate-grade lymphomas (*id.*). Thus, the methods disclosed in Breslow *et al.* reasonably suggest and motivate the treatment of lymphomas, including the instantly claimed diffuse large B-cell lymphomas.

Richon *et al.* disclose as applied to claims 30, 32-35, 37-40, 47, 49-56, 63-66 and 69-70 *supra*. Briefly, the reference discloses oral administration of SAHA at the instantly claimed doses for the treatment of TRX-mediated diseases, including diseases characterized by cellular hyperproliferation.

Thus, both Breslow *et al.* and Richon *et al.* disclose the administration of SAHA to patients to treat neoplastic diseases. The Merck Manual provides the motivation to use the methods disclosed in Breslow *et al.* and Richon *et al.* to treat lymphomas. As such, the instantly claimed methods of specifically treating B-cell lymphoma would have been *prima facie* obvious to one of ordinary skill in the art. B-cell lymphoma is a well-known neoplastic disease characterized by cellular hyperproliferation. Given the disclosures of Breslow *et al.* and Richon *et al.*, the skilled artisan would have been highly motivated to administer SAHA in the instantly claimed doses to treat a any neoplastic disease, including B-cell lymphoma. No unobviousness is seen in using prior art methods of orally administering SAHA to treat the specific cancer instantly claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 10/567,952

Claims 30, 32-35, 37-45, 47, 49-61, 63-68 and 70-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3-4, 10 and 16-20 of copending Application No. 10/567,952. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '952 application disclose methods of treating diffuse large B-cell lymphoma comprising orally administering SAHA. The specification of the '952 application is used as a dictionary to define "effective amount" as recited in the conflicting claims. At pages 58-59, the doses and dosing schedules as instantly claimed are disclosed. As such, the instantly claimed doses and dosing schedules are not patentably distinct from "an effective amount" as recited in the claims of the '478 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

U.S. Non-Provisional Application No. 11/492,478

Claims 30, 32-35, 37-45, 47, 49-61, 63-68 and 70-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 8 and 14-62 of copending Application No. 11/492,478. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '478 application disclose methods of treating diffuse large B-cell lymphoma comprising orally administering SAHA. The instantly claimed doses and dosing schedules are not patentably distinct from those recited in the claims of the '478 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

July 5, 2007

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PHYLLIS SPIVACK
PRIMARY EXAMINER
7/6/07